REMARKS

I. On entry of the foregoing amendments, claims 1-3, 7, 8, 22, 27, 31, 36, 40 and 49 are pending in the application, with claim 1 being the sole independent claim. Claim 1 is sought to be amended. Claims 7, 8 and 22 are identified as withdrawn. No new matter is added by way of the amendments. It is respectfully requested that the amendments be entered and considered.

It is believed that the amendments presented above will place the application in condition for allowance and/or in better form for appeal. (See 37 C.F.R. § 1.116(a).) It is respectfully requested that the amendments after Final Office Action be considered and entered. Reconsideration of the instant application is respectfully requested. The amendment to the claim was not introduced earlier because arguments and prior claim amendments were believed to have placed claim 1 in position for allowance.

Support for the amendment of claim 1 can be found, inter alia, throughout the specification, e.g., page 12, paragraph 3; page 17, last paragraph[1]; and page 27, last paragraph[2].

II. Applicants appreciate and acknowledge the Examiner's withdrawal of:

(i) the provisional rejection of claims 1-3, 31 and 36 on the ground of nonstatutory double patenting over claims 1-4, 9, 11 and 16 of Application No. 10/529,428;

(ii) the rejection of claims 1-3, 5 and 33 under 35 U.S.C. § 112, second paragraph;

(iii) the rejection of claims 1-3 and 27 under 35 U.S.C. § 102(b) as being anticipated by Leboulch et al. and as evidenced by Chu et al.;

(iv) the rejection of claims 1, 5 and 6 under 35 U.S.C. § 102(a) as being anticipated by Mori et al.;

(v) the rejection of claims 1, 5, 6, 31, 36 and 37 under 35 U.S.C. § 103(a) as being unpatentable over Leboulch et al. in view of Poeschla et al.;

(vi) the rejection of claims 41 and 42 under 35 U.S.C. § 103(a) as being unpatentable over Leboulch et al. in view of Poeschla et al. and further in view of Clark et al.; and

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1 The paragraph refers to Av3mEndo, which is a replication-defective viral vector.

2 The paragraph refers to BIVendostation, which is a replication-defective viral vector.

(vii) the rejection of claims 32-35 under 35 U.S.C. § 103(a) as being unpatentable over Leboulch et al. in view of Poeschla et al. and further in view of Mori et al.;

III. On page 4 of the Office Action, claims 1-3, 27, 31, 36 and 42 were provisionally rejected on the ground of nonstatutory double patenting over claims 1-3, 27, 28, 30-32, 38-41, 45 and 51-62 of U.S. Patent Application No. 10/080,797.

Applicants respectfully disagree. However to expedite prosecution, Applicants will consider filing a Terminal Disclaimer on indication of otherwise allowable subject matter.

IV. On page 5 of the Office Action, claims 1 and 31 were provisionally rejected on the ground of nonstatutory double patenting over claims 52-56 and 59 of U.S. Patent Application No. 10/910,293.

The Examiner stated on pages 5-6 of the Office Action that:

> "The applicant argues that he will "consider filing a Terminal Disclaimer on indication of otherwise allowable subject matter" (Remarks, filed 9/2/2009, page 4). The examiner acknowledges this comment. However, because the claims of the co-pending applications appear to still be obvious over each other, the examiner finds this argument unpersuasive." (Office Action, pages 5-6.)

That statement is incorrect. Section IV of the Remarks in the Amendment that was filed 2 September 2009, bridging pages 4-5, addresses the instant rejection by stating, "In view of the claim amendments incorporating elements of non-rejected claim 29 into the base claim, withdrawal of the rejection is in order."

Applicants assume that the above cited statement by the Examiner was simply an error since Applicants incorporated the subject matter of non-rejected dependent claim 29 into the rejected independent claim 1, rendering the rejection moot. Additionally, maintaining the instant rejection would actually be considered a new rejection, not necessitated by Applicants, and would have to be done in the form of a Non-Final Office Action.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the nonstatutory double patenting rejection.

V. On page 11 of the Office Action, claims 1, 31, 36 and 40 were rejected under 35 U.S.C. § 103(a) as being obvious over Leboulch et al. (WO99/26480)[3] in view of Poeschla et al. (U.S. Patent No. 6,555,107) and further in view of Brandt et al. (U.S. Patent No. 6,106,826).

Teaching Away and Cited Prior Art Does Not Teach Or Suggest All Claim Limitations

To establish prima facie obviousness of a claimed invention, an Examiner must show that all the claim limitations are taught or suggested by the prior art. In re Royka, 490 F.2d 981, 985 (Fed. Cir. 1974)

"The examiner concedes that neither Leboulch nor Poeschla teach subretinal injection." (Office Action, page 11)

The Brandt et al. patent mentions subretinal injection twice, but a review of the reference as a whole reveals that the Brandt et al. patent teaches away from the use of subretinal injection of a replication-defective viral vector.

For example, the Brandt et al. patent provides,

> "Previous attempts to deliver a gene to various parts of the eye have used adenoviruses, adeno-associated viruses, and Herpes simplex virus. So far, researchers have only been able to 'label' retinal cells, via subretinal injection, which causes retinal detachment in the area of the injection. (Brandt et al., column 4, lines 5-10)

That statement concludes that at the time, the only way to label retinal cells had been subretinal injection. However, that singular available means for labeling retinal cells was not without a significant side effect, namely, retinal detachment. Additionally, the "labeling" of a cell as described in the Brandt et al. patent was done with a non-secreted protein and is therefore distinct and less complex than having a cell of the eye properly express a secreted endostatin protein from an introduced replication-defective viral vector carrying a nucleic acid encoding same.

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[3] In making the rejection, the Examiner stated, on page 15 of the Office Action, that, "Leboulch et al. does not teach using lentiviral vectors . . ." Applicants note that Leboulch et al. mention lentiviral vectors, e.g., see claim 19 and Figure 3. Figure 3 depicts an HIV vector and HIV is a lentivirus.

Thus, the Brandt et al. patent teaches away from the claimed invention of using a replication-defective viral vector, since one skilled in the art at the time of the invention would have wanted to try to **avoid** retinal detachment.

In an attempt to rebut that clear teaching away, the Examiner pointed to the statement of Brandt et al. that reads, "… that 'subretinal or intravitreal injection of a number of growth factors, cytokines and neurotrophins . . . have been shown to restore specific function to retinal or retinal pigment epithelial cells' (col. 8, lines 29-32)." (Office Action, page 12)

However, that statement concerns only injection of protein and not of a replication-defective viral vector. The abstracts of both of Faktorovich et al. and LaVail et al. only refer to the injection of protein and not vector.

Therefore, the second reference to subretinal rejection in the Brandt et al. patent solely refers to the injection of protein and not to injection of vectors that express the protein. Those two options are clearly not interchangeable and have completely different biological requirements.

For example, injection of protein avoids any potential problems and uncertainty that might have been associated with expressing and secreting a protein from a vector at the desired area of the eye. Also, delivery of protein by injection is clearly a simpler and more predictive method than attempting to express a recombinant protein and to have the protein reach the diseased area in effective amounts. For example, (i) the nucleic acid of the vector must be able to enter cells in the area of the injection; (ii) the nucleic acid must travel to the appropriate cellular compartment (e.g., the nucleus) for transcription; (iii) the cells must be able to express the protein encoded by the nucleic acid; and (iv) the protein must be expressed in a manner (e.g., secretion) that allows the protein to exert an effect on the desired cells/tissue.

The retinal detachment described by Brandt et al. would not be expected to be an issue for protein delivery because the retinal cells are not necessary for the activity of the protein. In the case of a replication-defective viral vector, the retinal cells are required to produce and to secrete the protein encoded by the vector. If the retinal cells are detached,

the cells may not be "healthy" enough to express an effective amount of an endostatin. Moreover, even if the detached cells express and secrete the protein, the cells would be detached from the retina and thus, possibly not in a spatial position to allow the secreted protein to reach the blood vessels responsible for the leakage/edema.

In an attempt to address the fact that Brandt et al. teach that subretinal injection leads to retinal detachment, the Examiner stated:

> "As the 'wet' form of macular degeneration results from retinal edema and has the symptom of retinal detachment, a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema in patients with macular degeneration. The skilled artisan would be more focused on inhibiting the growth of blood vessels when administering therapeutic genes by subretinal injection. (Office Action, page 12)

Applicants respectfully disagree that a skilled artisan would not be concerned with retinal detachment caused by a subretinal injection. The Examiner made a conclusory statement and has cited no evidence to support the conclusion that, "…a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema...," via subretinal injection. (Office Action, page 12) Also, just because retinal detachment may be a symptom of a disease, does not mean that one skilled in the art would not be concerned about a procedure that results in retinal detachment, which may exacerbate the disease. In fact, one of the reasons to inhibit the blood vessels is to prevent retinal detachment.

Brandt et al. also provide a second teaching away that is unrelated to the above-mentioned retinal detachment. The Brandt et al. patent, as a whole, describes the use of replication-competent HSV based viral vectors in the eye. Brandt et al. make clear that replication-defective viral vectors are inferior and a replication-competent viral vector is superior for use in the eye. For example, Brandt et al. state:

> "Replication deficient viral vectors are frequently suggested for use in gene therapy because of safety concerns associated with using replication competent viruses. The problem with replication deficient viruses is that they infect one cell, and cannot propagate through a tissue or a larger area. Thus, if delivery is not efficient, only a limited number of cells are transformed. This is a serious limitation, particularly in the area of neural and ocular delivery, because replication is required for a virus to cross a synapse. (Brandt et al., column 3, lines 49-57, underlining added.)

Since Brandt et al. refer to replication-defective viral vectors as having serious limitations in the area of ocular therapy, one skilled in the art would have clearly been led away and discouraged from using a replication-defective viral vector as presently claimed. In fact, based on the teaching of Brandt et al., one skilled in the art would not have expected the claimed invention to be able to successfully inhibit retinal edema as required by the claims.

Therefore, the claimed invention cannot be considered to have been obvious at the time of the invention if there would have been a teaching away from the invention and there would not have been a reasonable expectation of success.

The Examiner referred to Brandt et al. as teaching "…'recombinant HSV vectors that express growth factors, cytokines and neurotrophins are suitable for treating ocular neuronal degenerative diseases and disorders, including ... macular degeneration' (col.8, lines 57-60)." (Office Action, page 12)

Applicants disagree that Brandt et al. "teach" that element. On a close inspection of Brandt et al., that quote appears to be mere speculation. For example, there is no experimental evidence in Brandt et al. to support that statement and Brandt et al. do not point to any evidence in the art to support that statement. In fact, the Brandt et al. patent contains no experimental evidence related to using a recombinant HSV vector to express any growth factors, cytokines or neurotrophins in eye tissue, let alone via a subretinal injection, or expressing an effective amount for treatment.

In contrast, the instant specification clearly demonstrates inhibition (treatment) of retinal edema by subretinally injecting a replication-defective viral vector encoding endostatin, for instance, see Example 7. Therefore, unlike the instant specification, Brandt et al. do not "teach" the use of HSV vectors to treat ocular diseases.

In summary, the Brandt et al. patent, as a whole, would not suggest subretinally injecting a replication-defective viral vector comprising an endostatin-encoding nucleic acid. Additionally, as discussed above, Brandt et al. do not teach subretinal injection of a replication-defective viral vector as claimed, and Brandt et al. teach away from the claimed invention. Neither Leboulch et al. nor Poeschla et al. cure those deficiencies or

negate the clear teaching away of the Brandt et al. patent. Hence based on the cited documents, a prima face case of obviousness has not been made, and the claimed subject matter would not have been obvious at the time of invention.

No Reasonable Expectation of Success

Additionally, the Examiner must show that there is a reasonable expectation of successfully combining the teachings of the references. In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991)

It can be seen that neither Leboulch et al. nor Poeschla et al. disclose subretinal injection of a replication-defective viral vector. The Examiner provided that Brandt et al., which makes passing mention of subretinal injection as a type of injection known in the art, allegedly cures that deficiency of the primary references. However, following the guidance provided by the In re Vaeck (947 F.2d 488 (Fed. Cir. 1991)) decision, the three documents can only be properly combined if on considering those documents, an artisan would have had a reasonable expectation of successfully obtaining the claimed invention.

However, the three cited documents do not provide a reasonable expectation of success with regard to treating retinal edema by subretinal injection of an effective amount of a replication-defective viral vector comprising an endostatin-encoding nucleic acid to an individual.

As discussed above, Brandt et al. provide at least 2 different reasons that teach away from the claimed invention and therefore, would cause those skilled in the art at the time of the invention to not expect success with the claimed invention. Additionally, prior to the present invention, other potential issues would have caused those skilled in the art to not have a reasonable expectation of success. Some of these issues are as follows.

For example, it was not known at the time of the invention if subretinal injection of a replication-defective viral vector encoding endostatin would transduce a sufficient number of ocular cells to express an effective amount of endostatin. For example, as discussed above, Brandt et al. refer to problems and serious limitations with replication-deficient viruses as vectors for ocular delivery.

Additionally, in Mori et al. (of record), an adenoviral vector expressing endostatin was used to transduce liver cells of a mouse. It was known that adenoviral vectors readily transduce a relatively large number of liver cells and thus express high levels of a transgene. For example, Figures 1A and 1B of Mori et al. demonstrate that endostatin expressed by liver reached levels of 10 μg/ml and higher in serum.

On the other hand, it was not known at the time of the invention if a subretinal injection of a replication-defective viral vector, which will typically transduce several orders of magnitude fewer cells than the i.v. injection of Mori et al., could achieve effective levels of endostatin expression.

Additionally, the results in Mori et al. were achieved with high levels of endostatin in serum. Endostatin expressed via a subretinal injection would not have been expected to achieve a significant level of endostatin in serum, let alone an effective local amount.

Moreover, it was not known if the endostatin produced via subretinal injection of a replication-defective viral could reach the same area of the eye as did the endostatin produced from liver cells as in Mori et al. Even if some endostatin from the subretinally injected endostatin vector reached the same area, it could not be known if an effective amount would reach that area of the eye.

Clearly, subretinal injection of a replication-defective viral vector will transduce completely different cell types that those transduced by i.v. injection in Mori et al. It was not known at the time of the invention if cells of the eye transduced by a subretinal injection would express effective amounts of endostatin. Furthermore, it was not known: (i) if endostatin would diffuse from the endostatin-expressing cells to the local area of retinal leakage; (ii) if cells would secrete endostatin from the correct "side" of the cells, since many cells of the eye are polarized; or (iii) if the endostatin would diffuse in the proper direction only to be flushed away, e.g., directly into the choroid, before effective levels could be reached at the site requiring treatment.

In addition, it was not known if cells of the eye, such as the retinal pigment epithelial cells or photoreceptor cells, could express and secrete endostatin without disrupting any of the highly specialized functions of those cells, and without causing significant pathology. It was not known (i) whether the endostatin produced by ocular cells would be functional and/or stable and

(ii) if endostatin would be degraded at a slow enough rate that would allow effective local levels of endostatin for treatment of retinal edema.

Finally, as noted above, Brandt et al., teach that subretinal injection causes retinal detachment in the area of injection. (Brandt et al., column 4, lines 7-10.) Prior to the claimed invention, it was not known if such detachment from injecting a replication-deficient endostatin viral vector would still allow for an effective amount of endostatin to be secreted from the cells, e.g., it was not known whether a significant number of the detached cells would die or if the cells would be too unhealthy to secrete effective amounts of endostatin.

Until the present invention, those skilled in the art did not have a reasonable expectation that the claimed invention could be practiced or utilized to treat retinal edema in an individual. Based on any one of the reasons above, at the time of the invention, there would not have been a reasonable expectation of success with regard to the claimed invention.

Thus, for those additional reasons, it is clear that the claimed invention would not have been obvious. Instead, the wholly unexpected observation that subretinal injection of a replication-defective viral vector expressing endostatin can yield effective levels of endostatin in the proper site(s) in the eye to treat retinal edema, speaks to the non-obviousness of the instant invention.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 103(a).

VI. On page 20 of the Office Action, claims 1-3, 27, 31 and 49 were rejected under 35 U.S.C. § 103(a) as being obvious over Rasmussen et al. (Drug Discovery Today, 2001, 6:1170-1175).

The Examiner cited page 1171, column 2, line 22, of Rasmussen et al. as teaching, "…that macular edema . . . is one of the diseases which can be treated by the methods described within the review article." (Office Action, page 20)

However, the mention of macular edema in Rasmussen et al. is in the "Introduction" section and Applicants were unable to find "edema" mentioned anywhere else in Rasmussen et al. Rasmussen et al. is limited to discussing anti-angiogenic therapies, and does not teach

treating edema. For example, Rasmussen et al. stated in the section titled, "Anti-angiogenic gene therapy" that:

> "Preclinical proof-of-principle studies, using either recombinant adenovectors to carry the genes encoding pigment epithelium-derived factor . . . and endostatin, or recombinant adeno-associated viruses carrying the transgene encoding for angiostatin, have recently been published and demonstrated that significant inhibition of neovascularization in various models of AMD or DR is feasible. (Rasmussen et al. page 1172, right column, lines 29-36, footnote references omitted and underlining added.)

Since Rasmussen et al. do not teach the treatment of retinal edema, that reference cannot be considered to teach all of the claim limitations. For that reason alone, the Examiner has not established a prima facie case of obviousness.

Additionally, the present specification describes the discovery that endostatin is capable of inhibiting retinal edema in addition to its ability to inhibit neovascularization. None of the cited documents disclose that characteristic of endostatin and therefore cannot teach the treatment of retinal edema with endostatin.

Furthermore, as discussed above, Brandt et al. teach away from the claimed invention and prior to the present invention, one skilled in the art would not have had a reasonable expectation of success in practicing the claimed invention.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 103(a).

VII. On page 23 of the Office Action, claim 36 is rejected under 35 U.S.C. § 103(a) as being obvious over Rasmussen et al. in view of Poeschla et al. (Office Action, page 23.)

Poeschla et al. was provided as allegedly teaching, "…non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors . . ." (Office Action, page 23)

However, that teaching does not cure the deficiencies of Rasmussen et al., as discussed in Section VI above.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant rejection under 35 U.S.C. § 103(a).

VIII. On page 25 of the Office Action, claims 1-3, 27, 31, 40 and 49 are rejected under 35 U.S.C. § 103(a) as being obvious over Rasmussen et al. in view of Nemerow et al. (U.S. Patent Application Publication No. 2002/0193327). (Office Action, page 25)

Nemerow et al. was provided as allegedly suggesting, "…gene therapy methods of treating retinal diseases . . . including macular edema . . . comprising subretinal injection . . . of viral vectors having inducible promoters . . . operably linked to a therapeutic gene. Furthermore, Nemerow teaches that endostatin can inhibit angiogenesis (parag. 0165)." (Office Action, page 25, underlining in original.)

However, that teaching does not cure the deficiencies of Rasmussen et al., as discussed in Section VI above.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of the rejections and early indication of allowance. If any questions remain, the Examiner is requested to contact the undersigned at the local exchange noted hereinbelow.

Respectfully submitted,

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